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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Tai-Shun Lin and William Prusoff
Serial No.	:	06/942,666
Filed	:	December 17, 1986
For	:	USE OF 3'-DEOXYTHYMIDIN-2'-ENE (3'-DEOXY-2', 3'- DIDEHYDROTHYMIDINE) IN TREATING PATIENTS INFECTED WITH RETROVIRUSES
Art Unit	:	181
Examiner	:	J. Tou

Hon. Commissioner of Patents
& Trademarks
Washington, D.C. 20231

Sir:

DECLARATION UNDER RULE 132

Colin McLaren declares that:

1. All statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

2. He is Director of Anti-Viral Clinical Research of Infectious Diseases in the Pharmaceutical Research and Development Division of Bristol-Myers Company located at Wallingford, CT. One of his responsibilities is to design and supervise the implementation of the clinical evaluation of antiviral drugs on behalf of Bristol-Myers Company by competent medical doctors at various medical research centers throughout the United States and the world. He holds a Ph.D. Degree in Virology awarded by University of Sheffield, England in 1971 and was awarded membership in the Royal College of Pathologists in 1985. He has 21 years of experience in this type of work. He is author or co-author of approximately 51 scientific publications in this field.

3. In his capacity as aforesaid Director of Anti-Viral Clinical Research of Infectious Diseases he has been actively involved with the clinical evaluation of the putative anti-AIDS compound d4T, 2',3'-didehydro-2', 3'-dideoxythymidine, which is the subject of the above-identified patent application.

4. Phase I clinical studies involving approximately 24 subjects treated with d4T were begun in 1989. The subjects each exhibited symptoms of HIV infection including subnormal CD4 antigen-bearing cell counts in the blood, the presence of the p24 antigen in the blood, and body weight loss. Treatment was by oral dosing. The purpose of these studies was to scrutinize the subjects for any indication of toxic effect resulting from drug administration, and to determine whether any change in the CD4, p24 antigen or weight loss parameters occurred which

reflect amelioration of the infection during treatment. These parameters are used as surrogate markers of antiviral effect which may relate to clinical efficacy. Interim results of these studies are now available.

5. CD4 Cell Counts: At a dosage of 2.0 mg/kg and 4.0 mg/kg of body weight per day of d4T, statistically significant increases in CD4 cell counts were observed after 2 weeks and after 6 weeks of treatment. The CD4 antigen-bearing cell counts is interpreted to reflect the number of T4 lymphocytes present in the circulating blood. It is postulated that a depletion of the T4 lymphocyte population is caused by the HIV infection. An increase in CD4 count after treatment from a sub-normal value before treatment is considered to be an encouraging sign of potential amelioration of HIV infection.

6. HIV p24 Antigen: Statistically significant reductions in the amount of p24 antigen in the bloodstream of the treated subjects were observed as follows:

2 mg/kg/day after 2 weeks and 6 weeks.

The p24 protein is an antigenic material which is a constituent part of the HIV particle. Its presence in the blood stream of a subject having an HIV infection is considered to be a direct reflection of the presence of the virus. A reduction in the p24 blood level of an HIV infected subject is regarded as an encouraging sign of potential amelioration of the infection.

7. Body Weight: Statistically significant weight gains after 2 weeks of treatment were observed at doses of 2 mg/kg and 4 mg/kg. After 6 weeks of treatment a statistically significant weight gain was observed for subjects treated with 2 mg/kg. A gain in weight following weight loss accompanying an HIV infection is regarded as a sign of improvement in the debilitated condition of the subject, and presumptively an amelioration of the infection.

8. Data demonstrating the anti-HIV effectiveness of ddC, d4T and AZT in vitro in various cell culture systems which are available in the files of Bristol-Myers company are summarized in the following table.

In Vitro Anti-HIV

Compound	Assay/Cell	ID_{50} (μm)[1]	TD_{50} (μm)[2]
ddC[3]	viability /ATH-8	0.1	32
	p24 antigen/CEM	<0.001	<0.1
d4T	p24 antigen/CEM-F	0.15	
AZT[4]	p24 antigen/CEM	0.45	54
	viability/ATH-8	6.0	32
	p24 antigen/CEM-F	0.1	

[1] Concentration producing 50% inhibition of viral replication

[2] Concentration producing 50% inhibition of cell viability

[3] ddC: 2',3'-dideoxycytidine

[4] AZT: 3'-azido-3'-deoxythymidine

Date Sept 22nd, 1989

Colin McLaren

Colin McLaren, Ph.D.

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